Comparison of the Four Formulas of Adjusting QT Interval for the Heart Rate in the Middle-Aged Healthy Turkish Men

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Objective: The aim of this study was to evaluate the QT intervals at different rest heart rates in healthy middle-aged Turkish men and to compare the known four QT adjusting methods for heart rate.

Methods and Results: The QT intervals were measured in electrocardiograms of 210 healthy men (mean age = 35–60 years). A curve relating QT intervals and heart rates from 45 to 135 beats/min was constructed for study population. Based on the formula of Bazett, Fridericia, and Framingham, adjusted QT intervals in these range of heart rates were separately estimated. An adjusting nomogram for different heart rates was created using a reference value, which was the measured QT interval at heart rate of 60 beats/min (QT_{No} = QT + correcting number). These four QT correction methods were compared with each other. The reference value of QT interval at heart rate of 60 beats/min was 382 ms. The relationship between QT and RR interval was linear ($r = 0.66$, $P < 0.001$). Nomogram method corrected QT interval most accurately for all the heart rates compared with other three adjusting methods. At heart rates of 60–100 beats/min, the equation of linear regression was $QT = 237 + 0.158 \times RR$ ($P < 0.001$). Bazett's formula gave the poorest results at all the heart rates. The formulas of Fridericia and Framingham were superior to Bazett's formula; however, they overestimated QT interval at heart rate of 60–110 beats/min ($P < 0.01$). At lower rates (<60 beats/min), all methods except nomogram method, underestimated QT interval ($P = 0.03$).

Conclusion: Among four QT correction formulas, the nomogram method provides the most accurately adjusted values of QT interval for all the heart rates in healthy men. Bazett's formula fails to adjust the QT interval for all the heart rates. **A.N.E. 2005;10(2):134–141**

QT interval; heart rate; correction method

The QT interval that is measured from the electrocardiography (ECG) represents the ventricular electrical systole.[1] It has been reported that in healthy people, there is a significant relationship between both all-cause deaths and deaths due to cardiovascular diseases and the prolonged QT interval.[2] It has also been suggested that the prolongation of QT interval may be a sign of cardiac and arrhythmic deaths in various patient populations.[3–5] Although several formulas have been studied in order to measure the accurate QT interval at different heart rates, the ideal formula for adjusting the QT interval has not been found yet.[6–9] Bazett's formula is the most commonly used formula.[6] There has been enough evidence that Bazett's formula fails to exactly adjust the QT interval; however, most of these studies include people from America, North and Central Europe.[7–11] In a study including Scandinavian men, a nomogram method based on the linear regression model gave more accurate results at all the heart rates.[9]

It is unknown whether QT interval varies in different races.[12,13] Therefore, our purpose is to compare the four formulas adjusting QT intervals for heart rates in healthy middle-aged Turkish men and to get the adjusted QT interval nomogram in this population.

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MATERIALS AND METHODS

Patients

Our study group was composed of 223 healthy men between 35 and 60 years of age who do not have any known illness. In the ECG, patients with right and left bundle branch block ($n = 5$), frequent supraventricular ($n = 3$) or ventricular premature beats ($n = 4$) (>10 beats/min), and delta waves ($n = 1$) were excluded from the study. After the exclusion, the remaining 210 patients constituted the main study group. The heart rates of the patients ranged from 48 to 135 beats/min. The group was then divided into four according to their heart rates. Group I: the heart rate below 60 beats/min; group II: the heart rate between 60 and 99 beats/min; group III: the heart rate between 100 and 119 beats/min; and group IV: the heart rate between 120 and 135 beats/min. No patients used any medications that might affect the QT interval.

Measuring of the QT Interval

Twelve-lead ECGs of the cases were recorded at a sensitivity of 10 mm/mV and a paper speed of 50 mm/s. Measurement was taken manually from the beginning of the QRS complex to the end of the T-wave where the terminal limb joined the TP baseline. D_2 and V_2 or V_3 derivations were used for the measurement. Three beats were measured in each 12-lead ECG. The mean of the results of these two derivations was calculated. The QT interval measurements were manually done by two cardiologist under a magnifier with the help of a ruler (millisecond-scaled). Similarly, in the leads that QT interval were calculated, the distance between the two R waves' peak point was measured by millisecond and the mean of them was calculated. Intrareader and interreader variability was tested by duplicate measurements of 20 randomly selected ECG of the study group. The QT interval was measured at heart rates changing between 48 and 135 beats/min. Besides this, the corrected QT intervals were calculated according to the known four correction formulas. These formulas were as following:

1. Bazett's formula: $QT_{Ba} = QT/RR\ 1/2$[6]
2. Fridericia's formula: $QT_{Fri} = QT/RR\ 1/3$[7]
3. Framingham's formula: $QT_{Fra} = QT + 0.156 \times (1 - RR)$[8], and
4. Nomogram method: $QT_{No} = QT +$ correction factor[9]

As proposed by Karjalainen et al.,[9] the QTNo of our study group was calculated as follows: the QT interval value of 382 ms at 60 beats/min was considered as a reference value.[1] On the analytical system, this measurement was recognized as X-axis, which corresponds to Y-axis value 0 in the figure. Heart rates varying from 48 to 135 beats/min were placed on the X-axis. The required QT interval adjustment for different heart rates was determined from the Y-axis. The deviations from the reference value of 382 ms at 60 beats/min (to both positive and negative sides) were assigned on the Y-axis, and a curve showing the QT correction number at different heart rates was then drawn. Using this curve, the deviations from reference value of 382 ms were considered as correction factor and the nomogram of corrected QT interval was constructed.

Statistical Analysis

The data were analyzed with the SPSS programme. The QT intervals at different subgroups of heart rate were presented as mean ± SD. At the first step, a relationship between age and QT interval was evaluated and there was no significant relation found in our study. Linear regression analysis was done in order to test whether there is a linear relationship between QT interval and heart rate. Having found the linear relation ($r = 0.66$, $P < 0.001$), we did the further analysis. The corrected QT intervals of the four different groups of heart rates were compared, and curves showing the relationship between QT interval, which was measured with four different methods, and heart rate were constituted. These were compared with one another. The difference between each measured QT interval and QT interval measured with correction method was accepted as the residual value. The squares of these residual values were estimated in the subgroups of heart rates. By dividing the total value of squared residuals into the number of cases belonging to the group, means of the squared residuals were obtained. The method having the smallest mean squared residuals was considered as the most accurate method. In the subgroups of heart rate, the means of corrected QT intervals that were calculated with four methods, and mean squared residuals were compared with "paired *t*-test." The

Table 1. The Measured and Calculated QT Intervals at Normal Heart Rates (60–100 beats/min)

Mean Age (years)	48.9 ± 9.9 (35–60)
Measured QT interval (ms)	357 ± 26
QT interval-Bazett (ms)	416 ± 27 (r = 0.906)*
QT interval-Fridericia (ms)	394 ± 24 (r = 0.971)*
QT interval-Framingham (ms)	396 ± 22 (r = 0.972)*
QT interval-nomogram (ms)	386 ± 23

*$P < 0.001$: The comparion of nomogram method (QT_{No}) with QT_{Bazett}, $QT_{Fridericia}$ vs $QT_{Framingham}$ methods and correlation coefficients.

correlation between the four methods was analyzed with "Spearman test." A P value <0.05 was considered statistically significant.

RESULTS

A total of 210 healthy men constituted the study population. The mean age was 48.9 ± 9.9 years (35–60 years). Heart rates varied from 48 to 135 beats/min. Intrareader and interreader variabilities had been tested by duplicate measurements of 20 randomly selected ECG of the study group. In relation to the QT interval measurements, intrareader and interreader variabilities were 2.3% and 3.1%, respectively, and two of them were below 5%. The smallest unit that could be calculated was 10 ms. The measured QT intervals were between 240 and 420 ms. The measured and calculated QT intervals at heart rate of 60–100 beats/min according to the four methods are shown in Table 1. Compared to the QTNo, the other corrected QT intervals were significantly longer ($P < 0.001$). In the whole group, there was a linear relationship between QT interval and heart rate ($r = 0.66$, $P < 0.001$), and the linear regression equation was $QT = 237 + 0.158 \times RR$ (standard error = 11 ms) (Fig. 1). QT interval was 382 ms at heart rate of 60 beats/min. The nomogram found by calculation of the deviations from this reference value is shown in Table 2. The values of QT interval measurement at different heart rate groups are shown in Table 3. For the different subgroups, the heart rate were as follows: $QT = 396.4 - 0.012 \times RR$ for group I, $QT = 238 + 0.151 \times RR$ ($r^2 = 0.28$, standard error = 15 ms) for group II, $QT = 79 + 0.428 \times RR$ interval ($r^2 = 0.13$, standard error 23 ms) for group III, and $QT = 469\ 0.339 \times RR$ interval for group IV. Among these equations, those of groups II ($P < 0.001$) and III ($P = 0.043$) were significant.

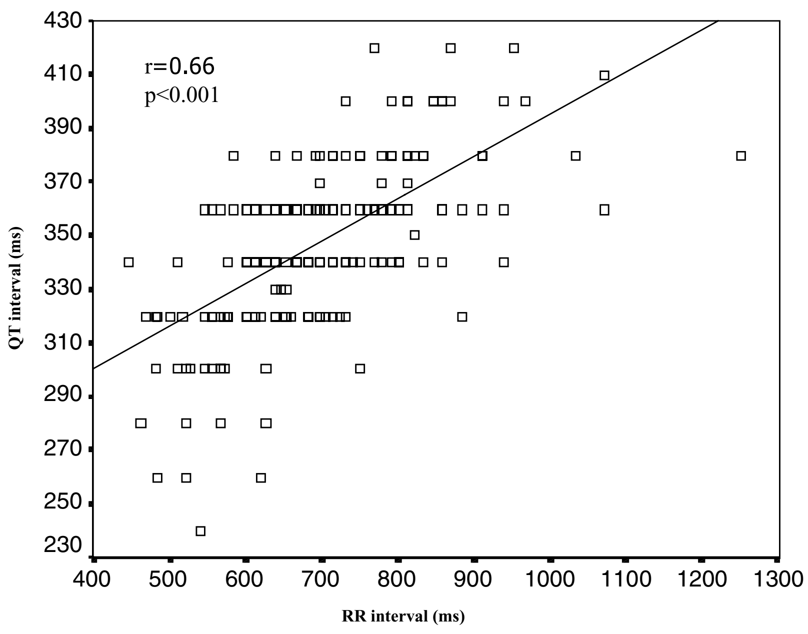

Figure 1. Linear relationship between heart rate and QT interval; linear regression equation was $QT = 237 + 0.158 \times RR$.

Table 2. Measured QT Intervals to Obtain a Heart Rate-Adjusted QT Value

Heart Rate (beats/min)	QT Correction (ms)	Heart Rate (beats/min)	QT Correction (ms)	Heart Rate (beats/min)	QT Correction (ms)
48	−24	78	28	108	75
49	−21	79	28	109	77
50	−19	80	31	110	77
51	−17	81	32	111	79
52	−15	82	34	112	80
53	−12	83	34	113	82
54	−10	84	37	114	83
55	−8	85	39	115	84
56	−6	86	40	116	86
57	−5	87	42	117	87
58	−3	88	43	118	89
59	−1	89	43	119	90
60	0	90	47	120	92
61	1	91	47	121	93
62	3	92	50	122	95
63	4	93	51	123	97
64	5	94	53	124	100
65	6	95	54	125	102
66	9	96	56	126	103
67	11	97	56	127	105
68	13	98	59	128	108
69	14	99	60	129	110
70	15	100	61	130	112
71	16	101	62	131	113
72	18	102	64	132	115
73	20	103	65	133	117
74	22	104	68	134	118
75	24	105	71	135	120
76	25	106	74		
77	27	107	74		

The Comparison of the Four Correction Methods

In Figure 2, the curves of the QT interval that were calculated with different four correction methods are shown. At all heart rates, QTNo showed the least deviation from the reference QT interval, which means that it corrected QT interval for different heart rates more accurately compared with others. Similarly, among the four methods, nomogram method gave the smallest mean squared residuls on an average (Table 4). When compared to the nomogram method, Bazett's formula underestimated QT intervals at lower heart rates ($P = 0.03$) and overestimated at normal and higher heart rates ($P < 0.01$). But Framingham and Fridericia methods were more reliable at normal heart rates than Bazett's method; however, they overestimated

Table 3. QT Intervals at Different Subgroups of Heart Rates

Groups of Heart Rate (beats/min)	n	Mean Heart Rate (beats/min)	QT Interval (ms)
Group I (<60)	4	54.5 ± 4.4	382.5 ± 20.6
Group II (60–99)	159	83.0 ± 9.5	354.9 ± 26.3
Group III (100–119)	39	106.4 ± 5.6	321.5 ± 29.5
Group IV (120–135)	8	126.4 ± 4.6	307.5 ± 26.1
Overall (48–135)	210	88.5 ± 15.3	347.4 ± 30.9

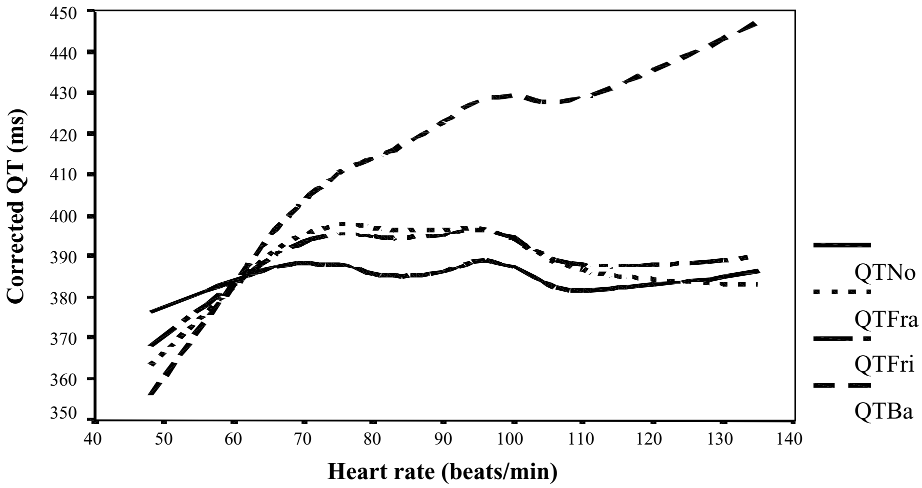

Figure 2. Curves of four formulas correcting QT interval at different heart rates.

the QT interval compared to the nomogram method ($P < 0.001$). On the other hand, these two formulae showed different QT interval values at lower and higher heart rates compared with the nomogram method (Table 5 and Fig. 2).

DISCUSSION

In the present study, we have found that among the four QT correction methods, nomogram method gave more accurate results than the others at a heart rate of 48–135 beats/min. We noticed that the commonly used Bazett's formula gave abnormal results at all the heart rates.

The Correlation Between Heart Rate and QT Interval

A linear relationship found between heart rate and QT interval was shown at 60–100 beats/min rates in healthy middle-aged men. The equation that we obtained from this study was $QT = 237 + 0.158 \times RR$. This result was in agreement with the results of Sagie et al.[8] and Karjalainen et al.[9] From the Framingham study, Sagie et al. had found the $QT = 228 + 0.147 \times RR$ equation in men between 29 and 62 ages (the mean age was 44 ± 9 years).[8] Karjalainen et al. had reported the $QT = 236 + 0.156 \times RR$ equation in men between the ages of 40 and 55 (the mean age was 47 years).[9] The number of articles studying QT interval at heart rates of <60 and >100 beats/min is limited. In the current study, we could not find a significant linear relationship at lower heart rates, but Karjalainen et al. had found the $QT = 277 + 0.116 \times RR$ equation.[9] The reason for this may be a very limited number of cases with heart rate <60 beats/min ($n = 4$) in the present study. We found the $QT = 79 + 0.428 \times RR$ equation between QT interval and RR at heart rates higher than 100 beats/min. However, Karjalainen et al. had found the $QT = 99 + 0.384 \times RR$ equation.[9] But we did not find a significant linear equation of heart rates >120 beats/min. The method is unable to explain the QT–RR relationship just one linear equation at lower or at higher rates.

Table 4. Mean of Squared Residual Values for Different Heart Rate Ranges and Different QT Interval Prediction Method

Groups of Heart Rate	QT Bazett	QT Fridericia	QT Framingham	QT Nomogram
Group I	1484	1365	1308	648
Group II	156	155	153	126
Group III	310	279	265	250
Group IV	1269	1257	1241	1023
Overall	241	240	239	205

Groups are same with Table 3.

Table 5. Calculated QT Interval According to Four Formulas in Different Heart Rate Groups

Groups	Measured QT (ms) (range)	QT_{Bazett} (ms) (range)	$QT_{Fridericia}$ (ms) (range)	$QT_{Framingham}$ (ms) (range)	$QT_{Nomogram}$ (ms) (range)
Group I	395 ± 25 (360–420)	373 ± 26 (340–409)	380 ± 25 (352–412)	375 ± 27 (342–412)	386 ± 24 (354–414)
Group II	357 ± 26 (260–420)	421 ± 28 (330–503)	398 ± 25 (305–466)	399 ± 23 (318–456)	389 ± 23 (311–452)
Group III	326 ± 27 (240–380)	434 ± 32 (326–514)	394 ± 31 (294–465)	392 ± 27 (310–450)	391 ± 26 (313–452)
Group IV	307 ± 22 (260–340)	447 ± 30 (373–510)	394 ± 27 (331–445)	388 ± 22 (339–425)	395 ± 23 (344–451)

Groups are same with Table 3.

Because the cardiac cycle length is not the only indicator for QT interval, it explains less than 50% of the variation in the QT interval.[8] It is also known that the autonomic nervous system has a significant effect on QT interval.[14] Moreover, healthy subjects' 24-hour-ECG records have shown that the relationship between QT interval and heart rate exhibits a subtstantial intra-subject stability. Whereas, QT–RR interval relationship among the different subjects have also exhibited a significant inter-subject variability.[11,15]

The Comparison of QT Correction Methods

The nomogram that we found in the middle-aged men was similar to the nomogram of the younger patients of previous reports.[9] It had been stated that the nomogram for younger subjects would also be valid for the middle-aged. For example, they found the correction constant to be 32 when the heart rate was 75 beats/min, while we found it to be 24. Although a significant linear relationship was found at normal heart rates, we did not see the same significant linear relationship at the lowest or highest limits of heart rates. However, significant linear relationship had been found in the previous study.[9] We speculated that these results are because of the limited number of cases of at very low and very high heart rates. According to our study, we found that the nomogram method was better than the other methods. We observed that at normal heart rates, both Framingham's linear regression formula[8] and Fridericia's cubic formula[7] were superior to Bazett's formula and give the results similar to nomogram method. Also, we found that the nomogram method is better than Bazett's. Bazett's formula gives corrected QT interval values that differ at all heart rates, so we think that calculating QT interval according to this formula would not be right. Our findings are supported by several previous studies as well.[8–11,15–18] Puddu et al. compared 10 mathematically different QT prediction formulas, including several complex multivariable equations and found that cubic root formula of Fridericia ranked best in the study sample of 881 middle-aged men.[10] This result was also confirmed by two other studies.[8,16] Fridericia's formula was better than that of Bazett's in our study as well. Yet, it was the second most suggested method after the nomogram method. However, when Rautaharju, Warren, and Calhoun analyzed the QT interval with 13 different formulas at all ages from new-borns to 75 year olds; they found that Fridericia's formula failed especially at high heart rates.[19] The reason for this contradiction could be that Rautaharju's study group was quite heterogenous and that the heart rates were at extreme levels. But in Framingham's study, it had been stated that the linear correction equation adjust the QT interval in both young and middle-aged men more reliably at normal (60–120 beats/min) heart rates.[8] However, just like us, Karjalainen et al.[9] had found that the nomogram method corrects QT interval most accurately in young men with heart rates between 40 and 120 beats/min. Furthermore, Karjalainen et al. showed that this result can also be applied to middle-aged healthy men. Between young and middle-aged groups, they also could not find a significant difference in the QT interval that was calculated according to the nomogram method. In spite of the fact that the data against it is on the increase, Bazett's formula still continues to be commonly used. The reason for this may be the fact that it is an easier method than other linear equations. It is clear that the QT interval values that were calculated according to this method will also give wrong results. Therefore, it is inevitable to be doubtful about the mortality studies that were calculated with Bazett's formula. We suggest that the nomogram method is as simple as Bazett's formula and more reliable than it. Today, although there are a lot of formulas that correct the QT interval according to heart rate, none of them could make QT interval independent from the heart rate.[6–11,14,15–18] Therefore, the problem of finding the best correction formula still remains.

What Should Be the Upper Limit of QT Interval?

Today, this question is of great importance because the present accepted upper limit (440 ms) was calculated with Bazett's formula, but it is clear that Bazett's formula fails to calculate the QT interval reliably (Fig. 2). Determining the upper limit is more important especially in drug studies[11] and in analyzing other family members of the individuals who have long QT syndrome or in diagnosing long QT syndrome.[20] For instance, in our study, 45 (20%) of the 210 male individuals had long QT interval according to Bazett's formula, whereas according to nomogram method, the number of individuals with a QT interval more than 440 ms was 1 (0.5%).

Study Limitations

It is well-known that the relationship between the QT interval and RR is affected by heart rate, age, and sex. Besides this, it has been stated that the relationship between QT interval and RR is different among individuals in recent years.[11] Because of this, it is clear that the equations that are obtained from all the subjects of the study group will not be applicable to each specific individual. This gains great importance in the studies testing drugs effect on the QT interval. In similar cases, the equation showing the correlation between QT and RR intervals must be found and this equation must be accepted as the reference point. In our study, age interval was relatively wide. However, we could not show a significant relationship between the QT interval and the age interval. In addition, a similar age interval had been used previously.[8] The number of cases with different heart rates from 60 to 100 beats/min is also limited. Lastly, QT calculations were done manually. Computer-supported ECG devices that do calculations automatically might have also been used, but no significant difference between these two methods has been recorded.[21] In addition to this, it is advised that the calibration must be frequently checked when doing automatic calculations.

In conclusion, Bazett's formula fails to correct the QT interval for heart rate, and calculating QT interval with this formula may result in inaccurate values. We believe that the nomogram method, which is not as complex as other linear equations, will give more reliable result.

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